SHORT COMMUNICATION

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Carbon–Phosphorus Bond Formation by Enantioselective Palladium-Catalyzed Allylation of Diphenylphosphine Oxide

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Keywords: Homogeneous catalysis / Palladium / Phosphorus / Allylation / Enantioselectivity / Regioselectivity

The enantioselective Pd-catalyzed allylation of diaryl-substituted allylic carbonates and diphenylphosphine oxide was investigated. This method gave allylic diphenylphosphine oxides in yields up to 95 % with 97 % *ee*. Pd-catalyzed allylation of (*E*)-methyl allyl carbonates with diisopropyl phosphonate was also examined.

Introduction

Pd-catalyzed asymmetric allylic substitution has become a powerful method for carbon–carbon and carbon–heteroatom (O, N, and S) bond construction.[1] In this context, such a reaction for carbon–phosphorus bond formation has been less reported.[2] Organophosphorus compounds are of great importance with regard to ligands,[3] functionalized materials,[4] and bioactive molecules.[5] As such, an efficient method for the synthesis of organophosphorus compounds with a chiral C–P center is highly desirable. Several strategies for C–P bond formation have emerged that employ P nucleophiles such as phosphines,[2d,6] phenylphosphine borane,[2e,7] phosphites,[8] and phosphine oxides.[9] In pioneering work, phosphine derivatives were examined in Pd-catalyzed asymmetric allylations;[2d] only diphenylphosphine gave a good outcome and other phosphines offered unsatisfactory results.[2d] In addition, both diphenylphosphine and diphenylphosphine oxide were applied in the catalytic phosphorus-Michael addition reaction.[6,9] We assume that diphenylphosphine oxide may be directly utilized in Pd-catalyzed allylation reactions for C–P bond formation. To the best of our knowledge, there are no reports of such an allylation of diphenylphosphine oxide. In contrast with diphenylphosphine,[2d] diphenylphosphine oxide has some advantages: one, diphenylphosphine oxide is not capable of coordinating with palladium; two, allylic phosphine oxides are not air sensitive; three, allylic phosphine oxide can be conveniently reduced with trichlorosilane ($HSiCl_3$).[10] Furthermore, the application of diphenylphosphine oxide may inhibit the formation of byproducts such as bis(diphosphine oxide).[11] In this paper, we report Pd-catalyzed allylic substitutions of diphenylphosphine oxide, which allow the synthesis of chiral allylic diphenylphosphine oxides.

Results and Discussion

We started our investigation with the reaction between (*E*)-1,3-diphenylallyl methyl carbonate (**1a**) and diphenylphosphine oxide (**2**) under palladium catalysis. Upon conducting this reaction in THF in the presence of tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP,[12] **L1**) at room temperature, the formation of *P*-allylated product **3a** was observed in a poor yield but with 98 %*ee*, and no bis(diphenylphosphine oxide) was obtained (Table 1, entry 1). Screening solvents revealed that toluene afforded a better yield than both THF and CH_2Cl_2 (Table 1, entries 2 and 3). Significantly, an improvement in the yield was achieved if a 5:1 ration of **1a**/**2** was used (Table 1, entry 4). Notably, this reaction is temperature sensitive in the 50–60 °C range (Table 1, entries 5–7). We were pleased to observe that the reaction could be performed at 55 °C and that it gave a better result (see Table 1, entry 6). Analysis of **1a** that was recovered upon completion of the reaction by HPLC on a chiral stationary phase revealed that it was racemic. At the same temperature, a decrease in the ration of **1a**/**2** led to a reduction in the yield, although high *ee* values were maintained (Table 1, entries 6, 8, and 9).

A range of chiral ligands such as **L1**, **L2**,[13] Josiphos ligand **L3**,[14] Trost's ligand **L4**,[15] and PHOX ligand **L5**[16] were investigated (Figure 1). BINAP (**L1**) and **L2** both gave excellent enantioselectivities (Table 1, entries 6 and 10). Ligand **L3** gave good results (Table 1, entry 11). Note that BINAP is an unsuitable ligand and that Josiphos **L3** is, however, the optimal ligand for the Pd-catalyzed asymmetric allylation of diphenylphosphine.[2d] Both **L4** and **L5** failed to promote this reaction (see Table 1, entries 10, 12, 13). Palladium catalysts including $Pd_2(dba)_3$, $[Pd(allyl)Cl]_2$, and $Pd(OAc)_2$ were then explored. $Pd_2(dba)_3$ led to the best

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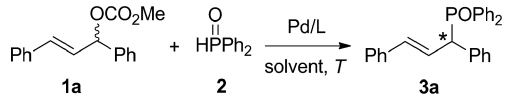
Table 1. Optimization of the reaction conditions for the enantioselective Pd-catalyzed allylation.[a]



Entry	Pd	Ligand	Solvent	T [°C]	**2**/**1**a	Yield[b] [%]	*ee*[c] [%]
1	$Pd_2(dba)_3$	**L1**	THF	25	1:1.2	15	98
2	$Pd_2(dba)_3$	**L1**	toluene	25	1:1.2	25	97
3	$Pd_2(dba)_3$	**L1**	CH_2Cl_2	25	1:1.2	15	90
4	$Pd_2(dba)_3$	**L1**	toluene	25	1:5	50	95
5	$Pd_2(dba)_3$	**L1**	toluene	50	1:5	65	93
6	$Pd_2(dba)_3$	**L1**	toluene	55	1:5	95	97
7	$Pd_2(dba)_3$	**L1**	toluene	60	1:5	98	90
8	$Pd_2(dba)_3$	**L1**	toluene	55	1:4	85	95
9	$Pd_2(dba)_3$	**L1**	toluene	55	1:3	75	93
10	$Pd_2(dba)_3$	**L2**	toluene	55	1:5	31	91
11	$Pd_2(dba)_3$	**L3**	toluene	55	1:5	80	87
12	$Pd_2(dba)_3$	**L4**	toluene	55	1:5	n.r.	–
13	$Pd_2(dba)_3$	**L5**	toluene	55	1:5	n.r.	–
14	$[Pd(allyl)Cl]_2$	**L1**	toluene	55	1:5	n.r.	–
15	$Pd(OAc)_2$	**L1**	toluene	55	1:5	n.r.	–

[a] Reaction conditions: Pd (5 mol-%), ligand (10 mol-%), **1a** (0.24–1 mmol), **3a** (0.20 mmol), solvent (2 mL), 25–60 °C. [b] Yield of isolated product; n.r.: no reaction. [c] Determined by HPLC analysis on a chiral stationary phase.

result, whereas $[Pd(allyl)Cl]_2$ and $Pd(OAc)_2$ were ineffective in this reaction (Table 1, entries 6, 14, 15). Diisopropyl phosphonate (**5**) instead of diphenylphosphine oxide (**2**) was tested under the optimal conditions, and the corresponding product was not observed.

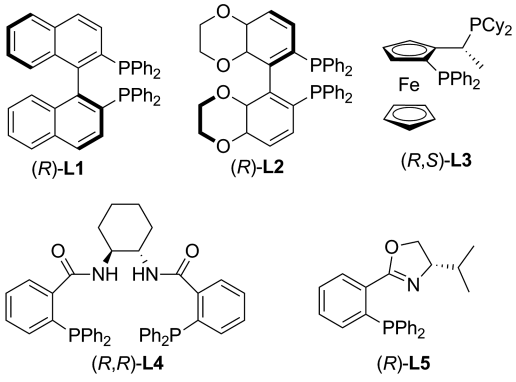
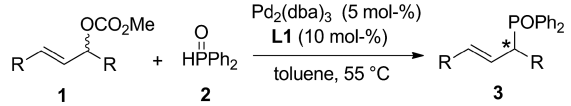


Figure 1. Ligands **L1**–**L5** evaluated for the titled allylic substitution.

Having established the optimized reaction conditions (Table 1, entry 6), the scope of allyl substrates **1** was examined. The results revealed the following factors: (1) (*E*)-1,3-Diphenylallyl methyl carbonate (**1a**) gave **3a** in excellent yield with excellent *ee* (Table 2, entry 1). (2) The reaction favored allyl substrates bearing electron-withdrawing groups, for example, substrates **1b**–**f** with 4-F, 4-Cl, 4-Br, 3-F, and 3-Cl groups on the phenyl ring provided *P*-allylated products **3b**–**f** in moderate to high yields with high levels of enantioselectivities, except for **1d**, which gave a moderate yield (Table 2, entries 2–6). (3) The reaction disfavored allyl substrates containing electron-donating groups; substrates **1g**–**h** with 4-Me and 3-Me groups on the phenyl ring led to *P*-allylated products **3g**–**h** in fair yields with good to high enantioselectivities (see Table 2, entries 7 and 8). These results suggest that **2** is a weak nucleophile and that it favors electrophilic substrates. (4) (*E*)-1,3-Di(naphthalen-1-yl)allyl methyl carbonate (**1i**) resulted in *P*-allylated product **3i** in moderate yield with moderate enantioselectivity (Table 2, entry 9). The *ortho* substituent effect was detrimental to the enantioselectivity, and this is in agreement with transition-metal-catalyzed allylations.[17] (5) In comparison to **1i**, (*E*)-1,3-di(naphthalen-2-yl)allyl methyl carbonate (**1j**) gave rise to *P*-allylated product **3j** in good yield with excellent enantioselectivity (Table 2, entry 10).

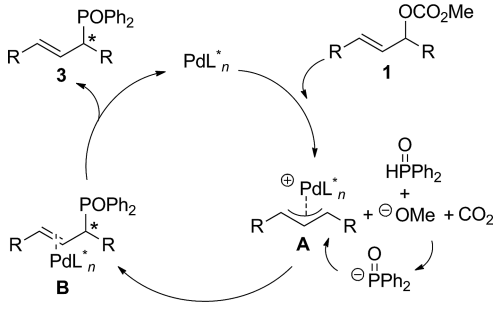
Table 2. Scope of (*E*)-allylic carbonates **1**.[a]



Entry	R	Product	Yield[b] [%]	*ee*[c] [%]
1	C_6H_5	**3a**	95	97
2	4-FC_6H_4	**3b**	75	94
3	4-ClC_6H_4	**3c**	92	90
4	4-BrC_6H_4	**3d**	62	94
5	3-FC_6H_4	**3e**	93	86
6	3-ClC_6H_4	**3f**	72	95
7	4-MeC_6H_4	**3g**	45	70
8	3-MeC_6H_4	**3h**	53	88
9	1-nathphyl	**3i**	65	–68
10	2-nathphyl	**3j**	60	–95

[a] Reaction conditions: $Pd_2(dba)_3$ (5 mol-%), L1 (10 mol-%), **1a** (1 mmol), **3a** (0.20 mmol), toluene (2 mL), 55 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

A possible reaction mechanism is proposed and is shown in Scheme 1. The oxidation addition of the Pd complex to **1** in toluene at 55 °C gives (π–allyl)palladium intermediate **A**, carbon dioxide (CO_2), and methoxide (^-OMe).[18] In the presence of ^-OMe, $HPOPh_2$ is converted into $^-POPh_2$;[9b,19] the latter attacks **A** to form intermediate **B**. Reductive elimination of **B** occurs to give **3** with regeneration of the Pd catalyst.

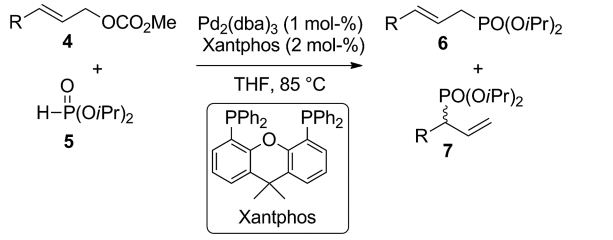


Scheme 1. Possible mechanism for the Pd-catalyzed allylic substitution of diphenylphosphine oxide (**2**).

We further extended the Pd-catalyzed allylic alkylation of P nucleophiles such as diisopropyl phosphonate to un-

symmetrical allyl carbonates, which gave allylic phosphinates.[5a] Upon using diisopropyl phosphonate (**5**) in such a reaction in the presence of $Pd_2(dba)_3$ (1 mol-%) and Xantphos[20] (2 mol-%) in THF at 85 °C, (*E*)-cinnamyl methyl carbonate (**4a**) and allyl carbonates **4b**–**g** with electron-donating groups (e.g., 4-Me and 3-MeO) or electron-withdrawing groups (e.g., 4-F, 4-Cl, 3-F and 3-CF_3) on the phenyl ring gave linear products **6a**–**g**[21] in moderate to excellent yields with high regioselectivities (Table 3, entries 1–7). Additionally, naphthyl- and thienyl-substituted allyl carbonates **4h** and **4i** also worked well (Table 3, entries 8 and 9). Unfortunately, (*E*)-methyl 5-phenylpent-2-enyl carbonate (**4j**) failed to undergo this reaction (Table 3, entry 10). We found that diphenylphosphine oxide (**2**) was ineffective in this reaction.

Table 3. Pd-catalyzed allylation of (*E*)-methyl allyl carbonates **4** with diisopropyl phosphonate (**5**).[a]



Entry	R	**6**/**7**[b]	Product, yield[c] [%]
1	C_6H_5	99:1	**6a**, 92
2	4-MeC_6H_4	99:1	**6b**, 95
3	4-FC_6H_4	99:1	**6c**, 71
4	4-ClC_6H_4	99:1	**6d**, 65
5	3-$MeOC_6H_4$	99:1	**6e**, 93
6	3-FC_6H_4	99:1	**6f**, 87
7	3-$CF_3C_6H_4$	99:1	**6g**, 65
8	2-nathphyl	99:1	**6h**, 75
9	2-thienyl	99:1	**6i**, 65
10	$PhCH_2CH_2$	–	**6j**, -

[a] Reaction conditions: $Pd_2(dba)_3$ (1 mol-%), xantphos (2 mol-%), **4** (0.2 mmol), **5** (0.24 mmol), THF (2 mL), 85 °C. [b] Determined by analysis of the crude product by ^1H NMR spectroscopy. [c] Yield of isolated product.

Conclusions

In summary, we developed the enantioselective Pd-catalyzed allylation of diphenylphosphine oxide to give allylation products in acceptable to excellent yields with moderate to excellent enantioselectivities. These are the first examples in which diphenylphosphine oxide is employed as a phosphorus source in Pd-catalyzed asymmetric allylic substitution reactions.

Experimental Section

General Procedure for the Pd-Catalyzed Allylation of Diphenylphosphine Oxide: A mixture of $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), the ligand (12.5 mg, 0.02 mmol), and toluene (2.0 mL) was stirred in a dry Schlenk tube filled with argon for 30 min; then, allylic carbonate **1** (134 mg, 1 mmol) and diphenylphosphine oxide (**2**; 40.4 mg, 0.20 mmol) were added. The mixture was stirred at 55 °C. Upon the completion of the reaction as monitored by TLC, the mixture was filtered through Celite, and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (ethyl acetate/petroleum ether = 1:1) to give product **3**, and the enantioselectivity was determined by HPLC analysis on a chiral stationary phase.

Supporting Information (see footnote on the first page of this article): Optimization of the reaction conditions for the Pd-catalyzed allylation reaction of **4** with **5**; copies of the ^1H NMR, ^{13}C NMR, ^{31}P NMR, and ^{19}F NMR spectra for **3** and **6**; and chiral HPLC chromatograms for racemic and enantiopure allylic diphenylphosphine oxides.

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